TREATMENT ADHERENCE BY PARTICIPANTS

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ADHERENCE IN CLINICAL TRIALS WHAT DO WE KNOW?

- ADHERENCE IS OFTEN HIGHER IN CLINICAL TRIALS DUE TO PARTICIPANT (OR CAREGIVER) SELECTION AND VOLUNTARY STATUS
- LACK OF ADHERENCE SIGNIFICANTLY AFFECTS SAMPLE SIZE AND TRIAL RESULTS
- ADHERENCE IS MOST OFTEN PREDICTED IN FIRST MONTH OF TRIAL PARTICIPATION
- METHODS TO DETECT NON-ADHERENCE AND PROMOTE ADHERENCE MUST BE EMPLOYED PRIOR TO RANDOMIZATION AND MONITORED THROUGHOUT STUDY PARTICIPATION

ADHERENCE IN CLINICAL TRIALS
WHAT DO WE KNOW?

- NO SINGLE STRATEGY IS EFFECTIVE IN ENHANCING ADHERENCE. MULTIPLE COGNITIVE, BEHAVIORAL AND SOCIAL SUPPORT STRATEGIES IMPROVE ADHERENCE
- POTENTIAL DROP-OUTS CAN BE RECOVERED THROUGH A SERIES OF MANEUVERS
- STUDIES INVOLVING SELF-ADMINISTERED TREATMENTS SHOULD BE MEASURING ADHERENCE SO IT CAN BE TAKEN INTO ACCOUNT AS A CO-VARIATE

CLINICAL TRIALS: ENHANCING ADHERENCE INVOLVES A PLANNED APPROACH

- CONSIDER ADHERENCE IN STUDY DESIGN
- DEVELOP WRITTEN GUIDELINES FOR
  - APPROPRIATE PARTICIPANT OR CAREGIVER SELECTION
  - PARTICIPATION AT CLINIC VISITS
  - MONITORING ADHERENCE TO STUDY REGIMENS INCLUDING COMPLETION OF STUDY QUESTIONNAIRES
  - STRATEGIES TO MAINTAIN ADHERENCE DURING COURSE OF TRIAL
  - STRATEGIES TO RETRIEVE “LOST” PARTICIPANTS
- MONITOR AND EVALUATE STUDY ADHERENCE THROUGHOUT COURSE OF TRIAL

FACTORS LIKELY TO IMPROVE PARTICIPANT ADHERENCE

STUDY DESIGN

- SHORTER STUDY DURATION
- CONTROLLED ENVIRONMENTS
- SIMPLICITY OF INTERVENTIONS

PARTICIPANT ENROLLMENT

- PT'S PERCEIVED BELIEF IN SUSCEPTIBILITY OR CONSEQUENCE OF CONDITION OR DISEASE
- PT'S PERCEIVED BENEFIT FROM INTERVENTION
- HIGHER LEVEL OF EDUCATION
- CLINIC SITE IN MULTI-CENTER STUDY
- STABILITY OF THE CAREGIVER
- *INFORMED PARTICIPANTS*

FACTORS LIKELY TO IMPROVE CAREGIVER ADHERENCE

- AGE AND HEALTH
- FAMILY SUPPORT SYSTEM
- RELATIONSHIP WITH PARTICIPANT
- BELIEF REGARDING PARTICIPANT'S CONDITION/DISEASE
- BELIEF IN THE PERCEIVED BENEFIT OF TREATMENT OR INTERVENTION

INFORMING STUDY PARTICIPANTS WHAT IS IMPORTANT?

- PT UNDERSTANDS CLINICAL TRIAL METHODOLOGY (BROCHURE, "INFORMATION FOR PATIENTS")
- PT IS ABLE TO REPEAT BACK TO YOU THEIR UNDERSTANDING OF TRIAL
- FAMILY MEMBERS ARE SUPPORTIVE
- PT IS PROVIDED A LISTING OF ALL FOLLOW-UP APPTS / CALLS
- CONTRACTS / WRITTEN AGREEMENTS ARE SIGNED
- A RELATIONSHIP IS FORMED WITH STUDY PERSONNEL (i.e. WARMTH, EMPATHY)
- CONTACT INFORMATION IS OBTAINED

WHAT IS IMPORTANT WHEN PARTICIPANT IS A MINOR OR INCOMPETENT?

PRIOR TO TRIAL

- DEFINE TREATMENT-RELATED RESPONSIBILITY OF CAREGIVER
- DEFINE INCLUSION/EXCLUSION CRITERIA
- DEVELOP CONSENT FORM
- SET CRITERION FOR ADHERENCE

MONITORING ADHERENCE TO STUDY REGIMENS

- FREQUENCY OF FOLLOW-UP VISITS / CONTACTS
- COMPLETION OF STUDY QUESTIONNAIRES
  (i.e. LOGS, CALENDARS, BASELINE, FOLLOW-UP)

MEDICATION TRIALS

- MEDICATION-TAKING BEHAVIORS
  - CHANGE IN DOSAGES, SIDE EFFECTS
  - REASON FOR CHANGE IN MEDS
- LABORATORY MEASURES
  - MARKERS, URINE ASSAYS
- PILL COUNTS
- MEDICATION EVENT MONITORS

MONITORING ADHERENCE TO STUDY REGIMENS

BEHAVIORAL TRIALS

- INTERVIEWS / RECORDS
  - DIET - 24 HOURS RECALL / 7 DAY FOOD RECORDS, FFQ's
  - EXERCISE - CALENDARS/LOGS - FREQENCY & INTENSITY OF EXERCISE, MONITORS
  - SYMPTOMS - FREQ. OF ANGINA / NITROGLYCERIN

HOW DO YOU ENSURE ADHERENCE? (PARTICIPANT/CAREGIVER/STUDY STAFF)

- DEVELOP A PLANNED APPROACH
- SCRIPT PROTOCOLS OF INTERVENTION STAFF
- TAPE/EVALUATE STAFF
- CONTINUE ONGOING QUALITY ASSURANCE MEASURES (OBSERVATIONS)
- TRACK PROCESS MEASURES
- ASK ABOUT ADHERENCE
- WRITE ABOUT YOUR OUTCOMES

IS A RUN-IN ADVANTAGEOUS?

- USED SUCCESSFULLY IN MEDICATION TRIALS
- NORMALLY A MINIMAL PERFORMANCE IS >80% OF MEDICATION ADHERENCE
- RESULTS IN 5 TO 10% OF SUBJECTS BEING ELIMINATED
- MAY ADD TO COST, PERSONNEL
- TEST-DOSING IS AN ALTERNATIVE TO RUN-IN

U.S. PHYSICIANS' HEALTH STUDY

- FACTORIAL DESIGN
- 3 MONTH RUN-IN: ASPIRIN AND BETA-CAROTENE
- 33,223 PHYSICIAN VOLUNTEERS
- 22,071 MET ADHERENCE CRITERIA
- ADHERENCE (RCT) 87.6% CONSUMING ONE MEDICATION AND 83.0% BOTH MEDICATIONS @ 57 MONTHS

STEERING COMMITTEE OF USPHS. N ENG J MED. 1989;321:129-135.

WHAT SUPPORTS ON-GOING OPTIMAL ADHERENCE?

CLINIC-VISITS

- PRE-APPOINTMENT REMINDERS OR TELEPHONE PROMPTS (CONFIRMATION 24-48 HOURS)
- OFFERING INCENTIVES i.e. MILEAGE REIMBURSEMENT, FLEXIBLE APPT SCHEDULES, PARKING PASSES, CHILDCARE, TRANSPORTATION, HOME VISITS
- CONTINUED INVOLVEMENT OF "REGULAR" STAFF (i.e. BUILD TRUST, MAINTAIN FOLLOW-UP, OFFER PROBLEM-SOLVING)

NATIONAL BETA-BLOCKER HEART ATTACK TRIAL

YEAR	PROPRANOLOL		PLACEBO	
	NUMBER OF VISITS REQUIRED	PERCENT OF VISITS COMPLETED*	NUMBER OF VISITS REQUIRED	PERCENT OF VISITS COMPLETED*
1ST YEAR	11,176	94.5	11,034	94.7
2ND YEAR	5,325	93.5	5,197	92.3
3RD YEAR	1,873	93.4	1,835	91.1
TOTAL	18,374	94.1	18,066	93.6

*INCLUDES INTERVIEWS WITHOUT EXAMINATIONS

BELL RL, et al. CONTROLLED CLIN TRIALS. 1985;6:89-101.

WHAT KEEPS PARTICIPANTS INVOLVED?

IN-BETWEEN CONTACTS

- WELCOME PACKETS WITH PERSONNEL NAMES AND CONTACT NUMBERS
- BIRTHDAY AND HOLIDAY CARDS
- MULTI-SITE NEWSLETTERS
- CARDS FOR HOSPITALIZED PARTICIPANTS
- INCENTIVES (i.e. CPR COURSE)

WHAT KEEPS CAREGIVERS INVOLVED?

FACILITATE CLINIC VISITS

- FLEXIBILITY IN SCHEDULING APPOINTMENTS
- TRANSPORTATION – EASE IN PARKING, NEAR PUBLIC TRANSPORTATION, TAXI REIMBURSEMENT
- CLINIC SITE IN SAFE, FAMILIAR ENVIRONMENT, NEAR HOME
- STABILITY OF CLINIC STAFF ON VISITS
- FEEDBACK ON PARTICIPANT'S STATUS/REGIMEN
- STAFF'S AWARENESS OF FAMILY STRUCTURE AND SUPPORT SYSTEM; USE OF THIS KNOWLEDGE IN HELPING CAREGIVER PROBLEM SOLVE RE ADHERENCE ISSUE

WHAT KEEPS CAREGIVERS INVOLVED?

BETWEEN CLINIC VISITS

- REGULAR CONTACT WITH STAFF (CARDS, NEWSLETTER, CALLS)
- SUPPORT GROUPS FOR CAREGIVERS
- RESPITE CARE
- ADHERENCE MONITORING PROCEDURES

DROPOUTS (%) AT FIRST AND LAST VISITS POSTRANDOMIZATION IN LONG-TERM STUDIES

STUDY	% DROPOUTS	TIME OF VISITS
BHAT	3.5, 15	1 MO., 36 MO.
AMIS	3, 6	1 MO., 36 MO.
U.K. PHYSICIANS	18, 30	6 MO., 72 MO.
CAPS	4, 9	3 MO., 12 MO.
LRC CPPT	1, 1.8, 6.1	2 WKS, 4 WKS, 7.4 YRS
B-MC*	2, 4, 0.6	2 WKS, 4 WKS, 7.4 YRS

AMIS = ASPIRIN MYOCARDIAL INFARCTION STUDY; BHAT = BETA-BLOCKER HEART ATTACK TRIAL; CAPS = CARDIAC ARRHYTHMIA PILOT STUDY; LRC-CPPT = LIPID RESEARCH CLINIC'S CORONARY PRIMARY PREVENTION TRIAL; UK PHYSICIANS = UNITED KINGDOM PHYSICIANS TRIAL OF PROPHYLACTIC ASPIRIN FOR CARDIOVASCULAR DISEASE MORTALITY.

PROBSTFIELD JL, et al. DROPOUTS FROM A CLINICAL TRIAL, THEIR RECOVERY AND CHARACTERIZATION: A BASIS FOR DROPOUT MANAGEMENT AND PREVENTION. IN: SHUMAKER SA, SHRON EB, OCKENE JK (EDS): THE HANDBOOK OF HEALTH BEHAVIOR CHANGE. NEW YORK: SPRINGER; 1990: 376-400.

RECOVERING DROPOUTS: SPECIFIC APPROACH

- COMPUTER-BASED SURVEILLANCE SYSTEM FOR MONITORING ADHERENCE
- SIX BASIC PRINCIPLES FOR COUNSELING
- PROCEDURES FOR REINSTITUTION OF PROTOCOL DURING DROPOUT RECOVERY

PROBSTFIELD JL, et al. AM J MED. 1989;80:777-784.

ENHANCING RECOVERY IN CORONARY HEART DISEASE (ENRICHD)

MULTI-CENTER RCT FUNDED BY NHLBI (8 CENTERS) INVOLVING 2,481 ACUTE M.I. PTS. (48% WOMEN, 34% MINORITY)

- MAJOR DEPRESSION OR
- MINOR DEPRESSION
- AND/OR LOW PERCEIVED SOCIAL SUPPORT

USUAL CARE OR INDIVIDUAL/GROUP COGNITIVE THERAPY OVER 6 MO.; PHARMACOTHERAPY FOR CONT. SEVERE DEPRESSION

PRIMARY ENDPTS – ALL CAUSE MORTALITY, RECURRENT NON-FATAL M.I.

THE ENRICHD INVESTIGATORS. AM J CARDIOL. 2001;88:316-322.

ANTIHYPERTENSIVE AND LIPID LOWERING TREATMENT TO PREVENT HEART ATTACK (ALLHAT)

SPONSORED BY NHLBI AND DEPARTMENT OF VETERANS AFFAIRS

RANDOMIZED PRACTICE-BASED TRIAL IN 42,500 HIGH RISK HYPERTENSIVE PATIENTS ($\geq$ 55 YRS) - 600 CENTERS

ANTIHYPERTENSIVE AND LIPID LOWERING TREATMENT TO PREVENT HEART ATTACK (ALLHAT)

HTN COMPONENT - DOUBLE-BLIND DESIGN TO DETERMINE WHETHER COMBINED INCIDENCE OF FATAL CHD AND NON-FATAL MI DIFFERS AMONG DIURETIC (CHLORTHALIDONE) AND 3 OTHERS - AMLODIPINE, LISINOPRIL OR DOXAZOSIN

LL COMPONENT - OPEN-LABEL TRIAL (20,000) IN MODERATELY HYPERCHOLESTEROLEMIC MEN AND WOMEN (≥ 55 YRS) TO DETERMINE WHETHER PRAVASTATIN WILL REDUCE ALL-CAUSE MORTALITY AS COMPARED TO USUAL CARE

WHAT'S IMPORTANT IN MONITORING ADHERENCE TO STUDY REGIMENS?

- NO SINGLE MEASURE OF ADHERENCE GIVES YOU A COMPLETE PICTURE
- NO WIDELY ACCEPTED DEFINITION OR CRITERION EXISTS FOR EITHER GOOD OR POOR ADHERENCE

FRIEDMAN LM, et al. FUNDAMENTALS OF CLINICAL TRIALS, 1998.

HINT:

ALWAYS ANTICIPATE WHAT THE REVIEWER WILL WANT TO KNOW WHEN YOUR TRIAL IS PUBLISHED. CAN YOU DEVELOP THE TABLES?

FACTORS AFFECTING ADHERENCE IN SPECIAL POPULATIONS

ELDERLY

- COGNITIVE FUNCTIONING
- POLY PHARMACY, DRUG/DRUG INTERACTIONS
- LIVING ALONE
- TRANSPORTATION
- LENGTH OF VISITS
- COMORBID CONDITIONS
- FAMILY SUPPORT

ETHNIC POPULATIONS

- SOCIAL STRUCTURE
- CULTURAL BELIEFS
- LITERACY